REMARKS/ARGUMENTS

In response to the Office Action of January 31, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 1 has been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The "Description of the Figures" section has been amended to add sequence identification numbers, clearly indicate that Figures 2, 3, 5 and 6 show the mass spectrum profiles of the disclosed biopolymer markers, and to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's).

Several protocols at pages 41-45 have been amended to properly identify trademark names (TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (line 12), page 42 (lines 3 and 18) and page 43 (lines 9 and 22) were underlined in the original disclosure and do not indicate amended text.

The paragraph at pages 46 was amended to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's). This paragraph was also amended to correct the grammatical format.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

No new matter has been added by the amendment to claim 1 made

herein.

Claim 1 has been amended to clearly indicate that the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) evidences a link to Alzheimer's disease. This language is supported by the specification as originally filed, for example at page 35, lines 14-18.

The Examiner notes that at page 11 of the Response, Applicant submits that claim 1 was amended to include the recitation "linked to Alzheimer's disease", but there appears to be no such recitation within the text of the claim, as presented on November 28, 2004.

Applicants note that at page 11 of the Response filed on November 28, 2004, Applicants indicate that the claims (including all pending claims) have been amended to recite that the claimed peptide is linked to Alzheimer's disease, see claim 39. The phrase "evidencing a link to Alzheimer's disease" is recited in claim 1 as presented herein.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain

equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Oath/Declaration

A new oath or declaration has been required by the Examiner because while the original oath filed on February 13, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature is omitted.

A new Declaration which is properly executed is filed herewith.

Rejection under 35 USC 101

Claim 1, as presented on November 29, 2004, stands rejected under 35 USC 101 because the claimed invention allegedly is not supported by either an apparent or disclosed specific and substantial credible utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner begins by stating that the instant application has provided a description of an isolated peptide, designated a "biopolymer marker". The Examiner alleges that the instant specification does not disclose a specific biological role for this peptide or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

The claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) is identified as a complement component C3 precursor peptide at page 46, lines 10-19 of the instant specification as originally filed. The instant specification contains an extensive discussion of the biological role of the complement system, see page 26, line 23 to page 29, line 11; and page 28, line 14 to page 29, line 11 specifically for the C3 complement component.

Thus, contrary to the Examiner's contention, the instant specification does disclose a specific biological role for the claimed peptide. Furthermore, even if the instant specification contained no such disclosure, the function of the complement system, including the C3 component, is well known in the art; see, for example, the attached definition of the "complement system",

from the Concise Encyclopedia Biochemistry and Molecular Biology, Third Edition, Walter de Gruyter Publishing, 1997; reference 1. The Examiner is reminded that a specification need not disclose what is well known to those skilled in the art.

The Examiner also alleges that the specification does not disclose the significance of the claimed peptide to a particular disease, disorder or physiological process which one would wish to manipulate for a desired clinical effect.

Page 27, lines 2-5 of the instant specification as originally filed discloses that the complement system is associated with Alzheimer's disease, cognitive disorders and Syndrome-X.

Thus, contrary to the Examiner's contention, the instant specification does disclose the significance of the claimed peptide to a particular disease, disorder or physiological process. Furthermore, even if the instant specification contained no such disclosure, the association of the complement system with disease, including Alzheimer's disease is well known in the art; see, for example, reference 1 and the attached abstract of Emmerling et al. Biochim Biophys Acta 1502(1):158-171 2000; reference 2. The Examiner is reminded that a specification need not disclose what is well known to those skilled in the art.

The rejected claim (claim 1) is not drawn to any manipulation of the peptide for a desired clinical effect. The Examiner is

reminded that the utility requirement is applicable to a claimed invention (see MPEP 2107.01).

The Examiner acknowledges that it is clear from the instant application that the protein described therein is a fragment of a larger molecule, complement C3 precursor protein, which has been isolated because of potential association of complement C3 precursor protein with Alzheimer's disease. There is little doubt that, after complete characterization, this peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 may be found to have a specific and substantial credible utility. The Examiner alleges that this further characterization is part of the invention and until it has been undertaken, Applicant's claimed invention is incomplete.

Applicants respectfully disagree with the Examiner's line of reasoning and assert that the claimed peptide (amino acid residues 2-14 of SEQ ID No:1) is useful for diagnosis and treatment of Alzheimer's disease since it was found to evidence a link to Alzheimer's disease (an "asserted" utility).

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the

claimed peptide (amino acid residues 2-14 of SEQ ID NO:1).

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, lines 10-19; and Figures 1 and 2).

The claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, Alzheimer's disease, thus the invention has a specific utility.

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

The risk for developing Alzheimer's disease increases with age. Thus, advances in diagnosis and treatment of Alzheimer's disease would greatly benefit the increasing elderly population. Considering that the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) represents an advance in Alzheimer's research, a "real-world" use, i.e., a substantial utility is attributable to the claimed peptide.

Accordingly, Applicants respectfully submit that since the invention has both specific and substantial utility no further characterization is required to show that the claimed peptide

(amino acid residues 2-14 of SEQ ID NO:1) satisfies the requirements as defined by 35 USC 101.

The Examiner alleges that the instant situation is directly analogous to that which was addressed in *Brenner v. Manson* (148 USPQ 689) in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility.

Applicants respectfully disagree with the Examiner's interpretation of *Brenner*. A complete reading reveals that the issue in *Brenner v. Manson* centers around a novel chemical process which produces a known compound (steroid). The "utility" question in this case is whether the practical utility of the compound produced by a chemical process is an essential element in establishing a *prima facie* case for the patentability of the process.

The utility and/or patentability of a process is not relevant to the situation in the instant application, as the examined claim, rejected under 35 USC 101, is not a process claim, it is a claim drawn to a biopolymer marker which evidences a link to Alzheimer's disease, thus directly benefitting to a public plagued by Alzheimer's disease. Furthermore, the instant specification does not attempt to evidence the utility of the claimed biopolymer

marker by comparison with structural analogs of the claimed peptide known to evidence a link to Alzheimer's disease. The data presented in the figures evidences the utility of the claimed peptide as linked to Alzheimer's disease, and thus, contrary to the Examiner's assertion, the instant invention does not suffer from an "absence of evidence supporting utility".

Accordingly, the situation in *Brenner v. Manson* is neither analogous to or relevant to the instant situation.

The Examiner asserts that the instant specification fails to explain either a biological significance of the claimed biopolymer marker in the development of Alzheimer's disease or the relationship between a polypeptide of SEQ ID NO:1 and "particular disease state." While it is not necessary that Applicant understands or discloses the mechanism by which the invention functions, in this case, in the absence of such an understanding the following questions must be answered, according to the Examiner. Is it "the up or down regulation of the marker relative to categorization of disease state"? Or is "the presence/absence" of the peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 indicative of a disease? The Examiner contends that because this critical information is not provided in the instant specification, as filed, a skilled practitioner would have to first use the claimed biopolymer marker as the object of future research

to establish the specific and substantial credible utility of the claimed peptide. However, it is a matter of law that the claimed invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

First, it has been established in preceding paragraphs that both the instant specification and the prior art explain the biological significance of the claimed biopolymer marker in the development of Alzheimer's disease.

The instant specification clearly indicates the relationship between the claimed peptide and a "particular disease state" (Alzheimer's disease). The claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) was identified as being linked to Alzheimer's disease through its differential expression in Alzheimer's disease and age matched controls; see Figure 1. The instant specification clearly discloses, at page 11, lines 9-20, the process for analyzing peptides identified by the disclosed methods and how to determine their relationship to a particular disease. Furthermore, such analysis is common practice in the art; see the attached article by Scott D. Patterson Physiological Genomics 2:59-65 2000, reference 3, especially the first paragraph on page 10 (of the

article as accessed from the internet) wherein an experiment directly analogous with the disclosed experiment is discussed. Figure 1 shows that the claimed peptide appears to be down-regulated in Alzheimer's disease; clearly indicating the relationship between the claimed peptide and Alzheimer's disease. This relationship identifies the claimed peptide as a potential marker for Alzheimer's disease. Thus, Applicants respectfully submit that no further experimentation is required to establish the utility of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1).

The Examiner asserts that a specification can meet the legal requirements of utility and enablement for a new peptide as long as the specification discloses at least one credible, specific and substantial asserted utility for the new peptide, or a well-established for the claimed peptide would be immediately obvious to the skilled artisan. The Examiner presents a hypothetical example which allegedly clarifies her position. For example, a hypothetical specification discloses that a claimed peptide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the peptide. The claimed peptide in the hypothetical example would not be rejected under 35 USC 101 and 112 first paragraph, as it has utility and is

enabled as a colon cancer marker. The Examiner asserts that such a fact pattern is not found in the instant case.

Applicants respectfully disagree with the Examiner's assertion.

The instant specification discloses that the claimed peptide is differentially expressed in Alzheimer's disease and age matched controls indicating its utility as a marker for Alzheimer's disease. The utility of the claimed peptide and the hypothetically claimed peptide were established by comparison of peptide of expression in a disease-state versus a non-disease state. Thus, Applicants respectfully assert that the fact pattern of the instant specification is, in fact, analogous to the fact pattern of the Examiner's hypothetical example.

Evidence will be sufficient, if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2107.02 VII).

The claimed peptide is identified as a fragment of complement component C3 precursor protein at page 46, lines 10-19 of the instant specification. Applicants assert that the claimed peptide is useful as a marker of Alzheimer's disease; which assertion is supported by the differential expression of the claimed peptide between Alzheimer's disease and age matched controls. Considering that complement activation is know to be involved in Alzheimer's

pathology (see attached abstract of Cooper et al. Immunological Research 21(2-3)159-65 2000; reference 4) one of ordinary skill in the art would believe that the claimed peptide is a useful marker of Alzheimer's disease more likely than not to be true.

Therefore, one of ordinary skill in the art would recognize the linkage between the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1); inflammation and Alzheimer's disease and thus would also find the suggestion of the claimed as a marker for Alzheimer's disease entirely reasonable.

Accordingly, based upon all of the above comments, Applicants assert that the claimed peptide has both a specific and a well established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on November 29, 2004, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, since the claimed invention is allegedly not supported by a either a clear asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

The Examiner continues to maintain the position that the instant specification fails to provide any evidence or sound

scientific reasoning that the instant claimed peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 is associated with any pathological condition, including Alzheimer's disease.

Applicants respectfully disagree with the Examiner's position and assert that the instant specification, as originally filed, fully supports the claim that an isolated biopolymer marker consisting of amino acid residues 2-14 of SEQ ID NO:1 evidences a link to Alzheimer's disease.

First, it has already been established by prior arguments in the instant Response that the claimed invention has both a specific and a well established utility.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

First, it is noted that it has already been established by the prior arguments in the instant Response that the claimed invention has both a specific and a well established utility.

An objective of the instant invention is to evaluate samples

containing a plurality of biopolymers for the presence of disease specific marker sequences which evidence a link to at least one specific disease state (see the instant specification as originally filed at page 35, lines 14-18). Applying this objective to the claims as currently pending, it is clear that the marker sequence is amino acid residues 2-14 of SEQ ID NO:1 and the disease state is Alzheimer's disease (see the instant specification as originally filed at page 46, lines 10-19). According to a definition obtained from the web site dictionary.com the term "link" refers to an association, and/or relationship (see attached document as accessed from the internet; reference 5). Thus, it can be said that the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) has an association with and/or a relationship to Alzheimer's disease.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) evidences a link to Alzheimer's disease; thus satisfying the precedent as set forth by the decision in *In re Brandstadter.*

The Examiner asserts that based on the limited information on how to conduct mass spectrometric analysis of a sample presented in the instant specification and on the analysis of Figures 1 and 4, one skilled in the art clearly would not be able to use the polypeptide of SEQ ID NO:1 as a biopolymer marker for any disease.

Applicants respectfully disagree with the Examiner's assertion.

At page 46, lines 10-13 of the specification as originally filed, SEQ ID NO:1 is identified as having a molecular weight of about 1682 daltons. The description of Figure 2 at page 37 indicates that the spectra depicted in the figure is that of ion 1682. The descriptions of the figures have been amended to clarify that the data shown in the figures is representative of the claimed and/or disclosed peptides. The spectra shown in Figure 2 was obtained from Band #C1 (resolved from a sample obtained from a patient age matched with an Alzheimer's patient) as shown in the gel of Figure 1. The gel in Figure 1 shows that Band #C1 appears to be strongly expressed in lanes containing samples obtained from patients age matched with the Alzheimer's patients as compared to expression of Band #2 present the corresponding location in lanes containing samples obtained from Alzheimer's patients. Thus, a difference is seen between two comparable samples (disease vs. non-disease), suggesting that the differentially expressed peptide is linked to Alzheimer's disease.

The specification, as originally filed, provides extensive information on how to conduct a mass spectrometric analysis of a sample. The Background of the Invention section provides a general overview of mass spectrometry and defines commonly used terms in

the field. Page 37, line 17 to page 40, line 12 summarizes the method by which the claimed peptide was identified. Specifically, page 39, line 3 to page 40, line 12 discloses how to analyze peptides collected from the gel by mass spectrometry.

Furthermore, the specification, as originally filed, provides a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 47, lines 3-14 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification

was obtained by carrying out mass spectrometry; for example, the figures disclose spectral profiles. Thus, contrary to the Examiner's assertion regarding the alleged limited disclosure, the specification, as originally filed, provides a precise protocol on how to conduct a mass spectrometric analysis on a sample and how to analyze the data (for example, data such as gels and spectral profiles) obtained by such an analysis.

Additionally, Applicants respectfully submit that such protocols are common practice. For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 3). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision and identification (see, for example, page 38, lines 13-17 of the instant specification as originally filed, and Figures 1 and 4). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 5 of Patterson, several automation processes are discussed in the

section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by differential expression.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those attempting to identify biomarkers.

For example, at page 10 of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(described by Ken Standing at the conference, page 6 of

Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two, diseases, providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, Weinberger uses the same approach (as the instant inventors) to interpreting data in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer. The Examiner insists that a proper biological marker is not one that is identified in a body fluid sample from an Alzheimer's patient but rather the one that is also not found in a body fluid sample from a control patient free of Alzheimer's disease as well as from a patient suffering from another, not Alzheimer's disease. Applicants respectfully point out to the Examiner that Weinberger linked seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease is commonly practiced in proteomics. Thus, Applicants respectfully contend that the Examiner has no basis to require such additional analysis in order to provide support for the enablement

of the instant invention.

Patterson discloses another study similar to that of the Applicants in method and interpretation (of data) at page 8 wherein potential markers of Alzheimer's disease were identified from cerebrospinal fluid.

Additionally a review article by Roland Kellner presents methods and experiments which are analogous those methods and experiments presented in the instant specification (see attached article by Kellner, Fresenius Journal of Analytical Chemistry 366:517-524 2000; reference 6).

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (amino acid residues 2-14 of SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are representative of proteins which are differentially expressed between the two samples types.

Figure 1 is a photograph of a gel showing the results of DEAE

resin (anion exchanging) column chromatography as carried out with a set of 9 samples; 4 serum samples from Alzheimer's disease patients (lanes 1-4, as read from the left), 4 serum samples from patients age matched with the Alzheimer's patients (lanes 5-8, as read from the left) and 1 sample of normal serum (pooled from different "normal" patients; lane 9, as read from the left). Lane 10 was reserved for molecular weight standard markers. Patient serum sample AG-AD-H-S-002 (lane 5) displays a band labeled AG-AD-H-S-D3(E)C1 and patient serum sample AD-H-S-004 (lane 1) displays a band labeled AD-H-S-D3(E)C2. Bands #C1 and #C2 appear at corresponding locations on the gel; however the amount of expression is decreased in band #C2 as compared with the amount of expression in band #C1. Band #C1 appears in a sample obtained from a patient age matched to an Alzheimer's patients and band #C2 appears in a sample obtained from an Alzheimer's patient.

The data presented in the figures, derived from the working examples, discloses that the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) is differentially expressed between Alzheimer's disease and a "normal" physiological state of patients age matched to the Alzheimer's patients, thus it can be reasonably predicted that such peptide is linked to Alzheimer's disease. Furthermore, the figures identify SEQ ID NO:1 and the specification discloses how such a sequence was identified as a notable sequence

in relation to Alzheimer's disease.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (amino acid residues 2-14 of SEQ ID NO:1) and Alzheimer's disease.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that the peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 is linked to Alzheimer's disease,

however, do not claim that such peptide is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed peptide is linked to Alzheimer's disease, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 7) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased patients; one of skill in the art would connect this peptide with potential diagnostic and/or therapeutics for Alzheimer's disease.

Thus, Applicants respectfully submit that since the

specification demonstrates a link between the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) and Alzheimer's disease and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of Alzheimer's disease, the requirement of "how to use" under 35 USC 122, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) and Alzheimer's disease to be reasonable.

Multiple studies indicate that a chronic inflammatory state mediated by activation of the complement system exists in the Alzheimer's disease brain (see US 5,532,219; McGreer et al. column 4, lines 25-40; reference 8; Cooper et al. Immunology Research 21(2-3):159-165 2000; reference 4; Emmerling et al. Biochim Biophys Acta 1502(1):158-171 2000; reference 2).

The claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) is identified as a fragment of complement component C3 precursor protein at page 46, lines 10-19 of the instant specification as originally filed. Figure 1 demonstrates that this claimed peptide appears to be down-regulated in Alzheimer's disease. This data is consistent with the studies indicating activation of complement in the pathology of Alzheimer's disease. The instant inventors thus

hypothesize that complement is processed in Alzheimer's disease. One of skill in the art, considering the known inflammatory mechanisms involved in the development and progression of Alzheimer's disease, would find such a hypothesis reasonable.

Therefore, one of ordinary skill in the art would recognize the linkage between the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1); inflammation and Alzheimer's disease and thus would also find the suggestion of SEQ ID NO:1 as a potential marker for Alzheimer's disease entirely reasonable.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:1 between Alzheimer's patients and patients age matched with the Alzheimer's patients evidences a link between the claimed peptide and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) and Alzheimer's disease and would further recognize how to use the claimed peptide as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

\\Ns2\SERVER\CLIENT FILES\2100-2199\2132 -Syn-X\2132_000090 - Complement C3 Precursor Biop\Amendments\2132_090_Response_1-31-05.wpd